REMARKS

As a preliminary matter, the Applicants wish to thank the Examiner for the courtesy of the interview that was extended to inventor Derek O'Hagan and the undersigned on August 21, 2002.

A. Claim Amendments

In view of the above amendment, claims 1-7, 9-16, 43-47, 52-54, 56-59 and 69-90 are pending herein. All pending claims fall within elected Group I.

Claims 17-19, 21-42, 48-51, 55 and 60-68 are deleted by the above amendment. Claims 17-19, 21-42, 48-51, and 60-68 are deleted, as they are drawn to non-elected Groups II-V. The deletion of claim 55 is discussed below.

Some pending dependent claims are directed to non-elected species. They have not been deleted at this time, however, because they will be entitled to consideration in the event of allowance of the generic independent claims from which they depend, as provided by MPEP 809.02(a).

Claims 69-90 are added by the above amendment. It is believed that no additional fees are due in connection with the addition of claims 69-90, due to the deletion of a sufficient number of claims herein. However, in the event that fees are due, the Office is authorized to charge the required amount to deposit account number 50-1047.

A separate sheet entitled "**Version with Markings to Show Changes Made**" is provided to illustrate the amendments made to the claims.

In the claim amendments, several multiple dependencies have been removed, so as to avoid having multiply dependent claims depend from other multiply dependent claims.

The amendment of claims 2, 10, 44, 52-54, 56 and 57, and the deletion of claim 55, reflect the fact that term "antigen" includes *inter alia*: (a) antigens containing polypeptides (for instance, proteins and glycoproteins--see, e.g., p. 9, lines 13 *et seq.*; see also, e.g., p. 13, lines 22 *et seq.* and originally filed claim 9, which lists glycoprotein antigens) as well as (b) polynucleotide antigens that encode immunogenic polypeptides (see, e.g., p. 10, lines 4-6).

Support for an antigen adsorbed on the surface of a microparticle in claims 1 and 43 can be found, for example, in originally filed claim 2.

Support for immunological adjuvant in the claims can be found, for example, in the specification at page 20, line 23.

Support for a microparticle composition comprising a pharmaceutically acceptable excipient in the claims can be found, for example, in originally filed claim 13.

Support for microparticles optionally containing entrapped antigen in the claims (and hence support for microparticles that do not contain entrapped antigen), can be found, for example, in the specification at page 19, lines 29 *et seq.*

Support for a double emulsion process in the claims is found, for example, at p. 18, lines 10-12 and p. 19, lines 1-2.

Support for an antigen derived from a pathogenic organism such as a bacterium or a virus in the claims can be found throughout the specification. See, e.g., page 13, lines 22-26 and p. 10, lines 7-8.

Support for hepatitis B virus antigen, *Haemophilus influenza* type B antigen, pertussis antigen, diphtheria antigen and tetanus antigen in the claims can be found, for example, in the specification at page 14, line 22, and page 16, lines 10-14.

Support for negatively and positively charged antigens in the claims can be found, for example, at p. 17, lines 1-9 of the specification.

Support for poly(D,L-lactide-co-glycolide) can be found, for example, in originally filed claim 5.

Support for a microparticle diameter between 500 nanometers and 10 microns in the claims is found, for example, at page 7, lines 8-13.

Support for an injectable composition in the claims can be found, for example, in the specification at page 22, lines 12-13.

B. Response to Office Action

1. Specification

An Abstract on a separate sheet is provided herein as required in the Office Action.

2. Rejection of claims 2-7, 10-16, 44-47 and 54-59, 35 U.S.C. 112, second paragraph

Claims 2-7, 10-16, 44-47 and 54-59 are rejected under 35 U.S.C. 112, second paragraph, as indefinite.

Claims 2, 3, 28, 44 and 45 are rejected, because they contain the following allegedly indefinite terms: "a transcription or translation mediator," "an intermediate in a metabolic pathway," "an immunomodulator," and "a pharmaceutical."

Claims 2 and 44 have been deleted.

As to claims 3 and 45, the above terms have been deleted in order to expedite prosecution in the present application, even though the Applicants believe that the metes and bounds of these terms would be understood by those of ordinary skill in the art.

Hence, it is respectfully submitted that claims 2, 3, 44 and 45 are presently in compliance with 35 U.S.C. 112, second paragraph.

Claim 28 is directed to a nonelected invention and has been deleted.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as indefinite based on the term "gp 120." Because claim 30 is directed to a nonelected invention, and because it is not within claims 2-7, 10-16, 44-47 and 54-59, which are presently rejected, it is assumed that the Office Action is referring to claim 10, which also contains this term. Claim 10 has been amended to recite "HIV gp120" based upon the Examiner's helpful suggestion. Hence, it is respectfully submitted that claim 10 is presently in compliance with 35 U.S.C. 112, second paragraph.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as indefinite based on the recitation of "a member." This expression has been deleted in claim 15 (as well as other claims), based on the Examiner's recommendation. Claim 15 is also rejected under 35 U.S.C. 112, second paragraph, as indefinite due to the abbreviations used therein. Claim 15 has been amended to recite the full name of the listed adjuvants, as suggested by the Examiner. Support for the amendment of claim 15 can be found, for

example, at p. 21 of the present specification. Hence, it is respectfully submitted that claim 15 is presently in compliance with 35 U.S.C. 112, second paragraph.

In view of the foregoing, reconsideration and withdrawal of the rejection of claims 2-7, 10-16, 44-47 and 54-59 under 35 U.S.C. 112, second paragraph are respectfully requested.

3. Rejection of claims 1-7, 11, 13, 14, 43-47 and 54-57, 35 U.S.C. 102(a)

Claims 1-7, 11, 13, 14, 43-47 and 54-57 are rejected under 35 U.S.C. 102(a) as anticipated by Levy et al. (WO 96/20698). This rejection is respectfully traversed for the reasons to follow.

Independent claim 43 is presently directed to a microparticle comprising (a) a biodegradable polymer; (b) a detergent selected from a cationic detergent and an anionic detergent; and (c) an antigen adsorbed on the surface of the microparticle.

Independent claim 1 is similar to claim 43, except that the polymer is specified to be selected from a poly(α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride, and a polycyanoacrylate.

The Applicants have found that providing a cationic and/or anionic detergent results in improved adsorption of the antigen to the biodegradable polymer. See, e.g., the present specification at page 3, line 19 to page 4, line 2. Without wishing to be bound by theory, it is believed that improved adsorption likely occurs due to charge interactions between the antigen and the anionic/cationic detergent. See, e.g., present specification at page 17, lines 1- 9.

Levy et al., on the other hand, teaches biodegradable controlled release nanoparticles as sustained release bioactive agent delivery vehicles. *See* Levy et al. Abstract. The nanoparticles are a core of biodegradable, biocompatible polymer. *See Id.* at page 6, lines 13 *et seq*. The polymeric core may have a bioactive agent or combination of agents incorporated, embedded, entrained or otherwise made part of the polymeric matrix comprising the nanoparticle core. *See Id.* at page 7, lines 1-3. The incorporated bioactive agent is released as the polymer hydrolyzes and dissolves, thereby biodegrading. *See Id.* at page 7, lines 3-4.

Hence, the overall teachings of Levy et al. are directed to particles having entrapped bioactive agents, which are made part of a polymer core and are released upon biodegradation of the polymer core.

The Office Action points to different passages within Levy et al., asserting that these passages teach various elements of the presently claimed invention. However, ven assuming solely for the sake of argument that elements of the presently claimed invention can be found at various points within the voluminous teachings of Levy et al., Levy et al. nonetheless does not describe a microparticle which comprises *the combination of* (a) a biodegradable polymer; (b) a detergent selected from a cationic detergent and an anionic detergent; and (c) an antigen adsorbed on the surface of the microparticle, as claimed.

Therefore, it is respectfully submitted that independent claims 1 and 43 are not anticipated by Levy et al.

Nor are claims 1 and 43 obvious in view of Levy et al.

First, it is respectfully submitted that there is no suggestion or motivation within Levy et al. to arrive at the invention as presently clamed in claims 1 and 43.

In this connection, it is respectfully submitted that due to the volume of the teachings in Levy et al., the chances of one or ordinary skill in the art arriving at the combination of elements as presently clamed in claims 1 and 43 are remote.

For instance, the Office Action asserts that "Levy et al. teach microparticles comprising an anionic or nonionic detergent (page 16 [*sic* page 15], first paragraph)." However, this paragraph lists nonionic surfactants in addition to anionic and cationic surfactants as surface modifying agents, with no indicated preference. Furthermore, in the pages leading up to this paragraph, an remarkably wide variety of additional surface modifying agents are proposed, including a large number of synthetic polymers, biopolymers, low molecular weight oligomers and natural products. See, e.g., Levy et al. at page 13, line 8 to page 14, line 20.

As previously noted, the Applicants have found that providing a cationic and/or anionic detergent results in improved adsorption of the antigen to the biodegradable polymer. Moreover, as discussed further below, the use of cationic or anionic detergents has been shown to result in improved adsorption, relative even to emulsion stabilizers and nonionic surfactants.

Levy et al., on the other hand, proposes the use of surface modifying agents for reasons other than improving surface antigen adsorption. For example, Levy et al. defines a "surface modifying agent" as "any chemical or biological compound, which may be a bioactive agent, having the property of altering the surface of nanoparticles so as to perform one or more of the following functions: to target binding of the nanoparticles to tissues or cells of living systems, to enhance nanoparticle sustained release properties, including retention at the site of administration, to protect nanoparticle-incorporated bioactive agents, to impart antithrombolytic effects, to improve suspendibility, and to prevent aggregation." *Id.* at page 13, lines 1-7.

It is respectfully submitted that these criteria would not lead one of ordinary skill in the art to choose, from among the myriad surface modifying agents disclosed in Levy et al., the presently claimed invention, which comprises a combination of (a) a biodegradable polymer; (b) a detergent selected from a cationic detergent and an anionic detergent; and (c) an antigen adsorbed on the surface of the microparticle.

Moreover, even assuming solely for the sake of argument that there is motivation in Levy et al. to arrive at the invention presently claimed in claims 1 and 43, it is respectfully submitted that Levy et al. is not enabling as a reference, because Levy et al. does not teach or suggest how to make the presently claimed invention.

Furthermore, and again assuming solely for the sake of argument that there is motivation in Levy et al. to arrive at the invention presently claimed in claims 1 and 43, it is respectfully submitted that one of ordinary skill in the art would not have reasonably expected success from the claimed combination.

Nonetheless, Applicants' efforts have been successful and surprisingly so. For example, Table 1 of the present specification shows significantly higher adsorption loads for p55gag on PLG (or poly[D,L-lactide-co-glycolide]) microparticles that contain anionic detergent (i.e., SDS, or sodium dodecyl sulfate) or cationic detergent (i.e., CTAB, or cetyl trimethyl ammonium bromide), relative to PLG microparticles that contain neither (i.e., PLG microparticles formed using PVA, or polyvinyl alcohol, as an emulsion stabilizer).

Table 1 also shows significantly higher adsorption loads for HCV core antigen on PLG microparticles that contain anionic detergent (i.e., SDS), relative to PLG

microparticles that do not (i.e., PLG microparticles containing PVA as an emulsion stabilizer).

See also, for example, Table 4 of the present specification which shows significantly higher adsorption loads for pCMVgp120 DNA on PLG microparticles that contain cationic detergent (i.e., CTAB), relative to PLG microparticles that do not (i.e., PLG microparticles formed using PVA as an emulsion stabilizer).

See also, for example, Table 5 of the present specification which shows significantly higher adsorption loads for E2 protein from Hepatitus C Virus (HCV) on PLG microparticles that contain cationic detergent (i.e., CTAB) or anionic detergent (i.e., SDS or NaOleate), relative to PLG microparticles that do not (i.e., PLG microparticles formed with PVA as an emulsion stabilizer, or formed with Pluronics P84 or L121, which are block copolymers of ethylene oxide and propylene oxide, also known as poloxamers, and are non-ionic surfactants).

Similar results are found, for example, in Table 7 for adsorption of listeriolysin protein.

It is noted that the teachings at pages 15 of Levy et al. do not give any indication that anionic and cationic surfactants are superior to other surface modifying agents, including nonionic surfactants, for any purpose, and certainly not for purposes of enhancing antigen adsorption to the particle surface.

In view of the above, it is respectfully submitted that independent claims 1 and 43 are neither anticipated by nor obvious in view of Levy et al. Moreover, claims 2-7, 9-16, 44-47, 52-54, 56-59 and 69-90, which are dependent upon these independent claims, are also patentable over Levy et al. for at least the above reasons as well.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-7, 11, 13, 14, 43-47 and 54-57 under 35 U.S.C. 102(a) as being anticipated by Levy et al. are respectfully requested.

4. Rejection of claims 1-7, 10, 11, 13, 14, 43-47 and 54-57 under 35 U.S.C. 103(a)

Claims 1-7, 10, 11, 13, 14, 43-47 and 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Moore et al. (Vaccine, 13/18: 1741-

1749, 1995) and Haynes et al. (AIDS Research and Retroviruses, 10, Suppl. 2:S42-S45, 1994).

As noted above, independent claim 43 is presently directed to a microparticle comprising (a) a biodegradable polymer; (b) a detergent selected from a cationic detergent and an anionic detergent; and (c) an antigen adsorbed on the surface of the microparticle. Independent claim 1 is similar to claim 43, except that the polymer is specified to be selected from a poly(α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride, and a polycyanoacrylate.

As also noted above, the teachings of Levy et al. do not render these claims obvious for a number of reasons including that one of ordinary skilled in the art would not be motivated by the teachings of Levy et al. to provide the combination of (a) a biodegradable polymer; (b) a detergent selected from a cationic detergent and an anionic detergent; and (c) an antigen adsorbed on the surface of the microparticle, that the combination is not enabled, and that there would be no reasonable expectation of success.

Moore et al. (which teaches the use of entrapped antigen and the use of PVA, rather than an anionic or cationic detergent) and Haynes et al. (which concerns gold microparticles to which DNA is bound by polymer) do not make up for the above-noted deficiencies in Levy et al. Hence, it is respectfully submitted that claims 1 and 43 are patentable over Levy et al. in view of Moore et al. and Haynes et al.

At least because they are directly or indirectly dependent upon claim 1 or claim 43, it is respectfully submitted that claims 2-7, 10, 11, 13, 14, 44-47, 54, 56 and 57 are likewise patentable over Levy et al. in view of Moore et al. and Haynes et al (claim 55 has been deleted).

For at least the above reasons, reconsideration and withdrawal of the rejection of claims 1-7, 10, 11, 13, 14, 43-47 and 54-57 under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Moore et al. and Haynes et al. are respectfully requested.

5. Rejection of claims 1-7, 10-15, 43-47 and 54-57 under 35 U.S.C. 103(a)

Claims 1-7, 10-15, 43-47 and 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Cleland et al. (U.S. Patent No. 5,643,605).

As noted above, independent claims 1 and 43 are presently patentable over Levy et al. Moreover, Cleland et al. (which appears to teach microspheres having encapsulated antigen, rather than adsorbed antigen as indicated in the Office Action) does not make up for the above-noted deficiencies in Levy et al. Hence, it is respectfully submitted that claims 1 and 43 are patentable over Levy et al. in view of Cleland et al.

At least because they are directly or indirectly dependent upon claim 1 or claim 43, it is respectfully submitted that claims 2-7, 10-15, 44-47, 54, 56 and 57 are likewise patentable over Levy et al. in view of Cleland et al. (claim 55 has been deleted).

Reconsideration and withdrawal of the rejection of claims 1-7, 10-15, 43-47 and 54-57 under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Moore et al. and Haynes et al. are thus respectfully requested.

6. Rejection of claim 16 under 35 U.S.C. 103(a)

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Cox et al. (U.S. Patent No. 5,902,565) or (b) Levy et al. in view of Cleland et al. and further in view of Cox et al.

As noted above, independent claim 1 is presently patentable over Levy et al. Moreover, as also noted above, Moore et al., Haynes et al. and Cleland et al. do not make up for the above-noted deficiencies in Levy et al. The same is true of Cox et al., which is cited for its teaching of aluminum phosphate as an adjuvant. Hence, it is respectfully submitted that claim 1 is patentable over these references.

At least because it depends upon claim 1, it is respectfully submitted that claim 16 is likewise patentable over the above references. Reconsideration and withdrawal of the rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Cox et al. or (b) Levy et al. in view of Cleland et al. and further in view of Cox et al. are thus respectfully requested.

7. Rejection of claim 58 under 35 U.S.C. 103(a)

Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Carlo et al. (U.S. Patent No. 4,413,057) or (b) Levy et al. in view of Cleland et al. and further in view of Carlo et al.

As noted above, independent claim 1 is presently patentable over Levy et al. Moreover, as also noted above, Moore et al., Haynes et al. and Cleland et al. do not make up for the above-noted deficiencies in Levy et al. The same is true of Carlo et al., which teaches extraction of polysaccharides from bacteria using hexadecyltrimethylammonium hydroxide as a cationic detergent. Hence, it is respectfully submitted that claim 1 is patentable over these references.

At least because it depends upon claim 1, it is respectfully submitted that claim 58 is likewise patentable over the above references. Reconsideration and withdrawal of the rejection of claim 58 under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Carlo et al. or (b) Levy et al. in view of Cleland et al. and further in view of Carlo et al. are thus respectfully requested.

8. Rejection of claim 59 under 35 U.S.C. 103(a)

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et al. in view of Moore et al. and Haynes et al. and further in view of Macfarlane (U.S. Patent No. 5,010,1834,413,057) or (b) Levy et al. in view of Cleland et al. and further in view of Macfarlane.

As noted above, independent claim 1 is presently patentable over Levy et al. Moreover, as also noted above, Moore et al., Haynes et al. and Cleland et al. do not make up for the above-noted deficiencies in Levy et al. The same is true of Macfarlane, which teaches the use of sodium dodecyl sulfate as an anionic detergent for purifying DNA. Hence, it is respectfully submitted that claim 1 is patentable over these references.

At least because it depends upon claim 1, it is respectfully submitted that claim 59 is likewise patentable over the above references. Reconsideration and withdrawal of the rejection of claim 59 under 35 U.S.C. 103(a) as being unpatentable over either (a) Levy et

al. in view of Moore et al. and Haynes et al. and further in view of Macfarlane or (b) Levy et al. in view of Cleland et al. and further in view of Macfarlane are thus respectfully requested.

CONCLUSION

Applicants submit that claims 1-7, 9-16, 43-47, 52-54, 56-59 and 69-90 are in a condition for allowance, early notification of which is earnestly solicited. The Examiner is encouraged to telephone the Applicant's attorney at (703) 433-0510 in order that any outstanding issues be resolved.

The Office is authorized to charge the $400.00 two-month extension fee, as well as any other fees required to deposit account number 50-1047.

Please continue to send all correspondence to Chiron Corporation.

Respectfully submitted,

David B. Bonham
Registration No. 34,297

Attorney for Applicant
Mayer Fortkort & Williams, PC
251 North Avenue West, 2nd Floor
Westfield, NJ 07090
Tel.: 703-433-0510
Fax: 703-433-2362

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Marjorie Scariati

Typed or Printed Name of Person Mailing Correspondence

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IN THE CLAIMS:

1. (Twice Amended) A microparticle ~~having an adsorbent surface, said microparticle~~ comprising:

a polymer selected from the group consisting of a poly(α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride, and a polycyanoacrylate; ~~and~~

a detergent selected from a cationic detergent and an ~~or~~ anionic detergent; and

an antigen adsorbed on the surface of said microparticle.

2. (Twice Amended) The microparticle of claim 1, wherein said antigen is selected from an antigen comprising a polypeptide and an antigen comprising a polynucleotide. ~~further comprising a first biologically active macromolecule adsorbed on the surface thereof, wherein the first biologically active macromolecule is at least one member selected from the group consisting of a polypeptide, a polynucleotide, a polynucleoside, an antigen, a pharmaceutical, a hormone, an enzyme, a transcription or translation mediator, an intermediate in a metabolic pathway, an immunomodulator, and an adjuvant.~~

3. (Twice Amended) The microparticle of ~~claim 2~~ claim 1, further comprising an additional ~~a second~~ biologically active macromolecule encapsulated within said microparticle, wherein the ~~second~~ additional biologically active macromolecule is selected from ~~is at least one member selected from the group consisting of~~ a polypeptide, a polynucleotide, a polynucleoside, an antigen, ~~a pharmaceutical,~~ a hormone, an enzyme, ~~a transcription or translation mediator, an intermediate in a metabolic pathway, an immunomodulator,~~ and an immunological adjuvant.

4. (Amended) The microparticle of claim 1, ~~any of claims 1-3,~~ wherein the ~~microparticle comprises a~~ poly(α-hydroxy acid) is selected from ~~the group consisting of~~ poly(L-lactide), poly(D,L-lactide) and poly(D,L-lactide-co-glycolide).

5. (Amended) The microparticle of claim 1, ~~any of claims 1-4,~~ wherein the polymer is ~~microparticle comprises~~ poly(D,L-lactide-co-glycolide).

6. (Amended) The microparticle of claim 1, ~~any of claims 1-5,~~ wherein the detergent is a cationic detergent.

7. (Amended) The microparticle of claim 1, ~~any of claims 1-5,~~ wherein the detergent is an anionic detergent.

9. (Twice Amended) The microparticle of claim 1, ~~any of claims 2-7,~~ wherein the ~~first biologically active macromolecule is an~~ antigen is selected from ~~the group consisting of~~ an HIV gp120 antigen, an HIV gp160 antigen, an HIV p24gag antigen, an HIV p55gag antigen, and a Influenza A hemagglutinin antigen.

10. (Twice Amended) The microparticle of claim 1, ~~any of claims 2-7,~~ wherein the ~~first biologically active macromolecule is~~ antigen comprises a polynucleotide which encodes an HIV gp120 antigen.

11. (Twice Amended) The microparticle of claim 3, ~~any of claims 3-7, 9 and 10,~~ wherein the additional ~~second~~ biologically active macromolecule is an immunological adjuvant.

12. (Twice Amended) The microparticle of claim 11, wherein the immunological adjuvant is an aluminum salt.

14. (Twice Amended) A microparticle composition comprising a microparticle according to any of claims 1, 2, 4-7, 9 and ~~, 10, and 13~~ a pharmaceutically acceptable excipient, and ~~further comprising~~ an immunological adjuvant.

15. (Amended) A microparticle composition of claim 14, wherein the immunological adjuvant is ~~a member~~ selected from ~~the group consisting of~~ CpG oligonucleotides, E. coli heat-labile toxin-K63 (LTK63), E. coli heat-labile toxin-R72 (LTR72), monophosphorylipid A (MPL), and an aluminum salt.

16. (Amended) A microparticle composition of claim 15, wherein the ~~adjuvant is an~~ aluminum salt ~~which~~ is aluminum phosphate.

43. (Twice Amended) A microparticle ~~having an adsorbent surface, said microparticle~~ comprising:

a biodegradable polymer; ~~and~~

a detergent selected from a cationic detergent and an ~~or~~ anionic detergent; and

an antigen adsorbed on the surface of said microparticle.

44. (Twice Amended) The microparticle of claim 43, wherein said antigen is selected from an antigen comprising a polypeptide and an antigen comprising a polynucleotide. ~~further comprising a first biologically active macromolecule adsorbed on the surface thereof, wherein the first biologically active macromolecule is at least one member selected from the group consisting of a polypeptide, a polynucleotide, a polynucleoside, an antigen, a pharmaceutical, a hormone, an enzyme, a transcription or translation mediator, an intermediate in a metabolic pathway, an immunomodulator, and an adjuvant.~~

45. (Amended) The microparticle of claim 44, further comprising an additional ~~a second~~ biologically active macromolecule encapsulated within said microparticle, wherein the ~~second~~ additional biologically active macromolecule is selected from ~~is at least one member selected from the group consisting of~~ a polypeptide, a polynucleotide, a

polynucleoside, an antigen, ~~a pharmaceutical,~~ a hormone, an enzyme, ~~a transcription or translation mediator, an intermediate in a metabolic pathway, an immunomodulator,~~ and an immunological adjuvant.

46. (Amended) A microparticle composition comprising a microparticle of any of claims 43-45 ~~44-45~~ and a pharmaceutically acceptable excipient.

47. (Amended) A ~~The~~ microparticle composition comprising a microparticle according to any of claims 43 and 44, ~~46,~~ a pharmaceutically acceptable excipient, and ~~further comprising~~ an immunological adjuvant.

52. (Amended) The microparticle of any of claims 1, 3, 4, 5, 6, 7 and 11, wherein the ~~first biologically active macromolecule~~ antigen comprises ~~is~~ a polypeptide.

53. (Amended) The microparticle of claim 52, wherein the polypeptide is ~~first biologically active macromolecule is a polypeptide antigen~~ selected from ~~the group consisting of~~ HIV ~~antigens~~ polypeptides, hepatitis B virus polypeptides, hepatitis C virus ~~antigens~~ polypeptides, *Haemophilus influenza* type B polypeptides, pertussis polypeptides, diphtheria polypeptides, tetanus polypeptides, and influenza A virus ~~antigens~~ polypeptides.

54. (Amended) The microparticle of any of claims 1, 3, 4, 5, 6, 7 and 11, wherein the ~~first biologically active macromolecule is~~ antigen comprises a polynucleotide.

56. (Amended) The microparticle of claim ~~55~~ 54, wherein the antigen comprises ~~polynucleotide encoding the antigen is~~ a plasmid DNA molecule.

57. (Amended) The microparticle of claim ~~55~~ 54, wherein the polynucleotide encodes a polypeptide ~~antigen is~~ selected from ~~the group consisting of~~ HIV ~~antigens~~ polypeptides, hepatitis B virus polypeptides, hepatitis C virus ~~antigens~~ polypeptides,

Haemophilus influenza type B polypeptides, pertussis polypeptides, diphtheria polypeptides, tetanus polypeptides, and influenza A virus ~~antigens~~ polypeptides.

Add Claims 69-90.

Delete Claims 17-19, 21-42, 48-51, 55 and 60-68.